

General

Guideline Title

Radiation therapy for glioblastoma: an ASTRO evidence-based clinical practice guideline.

Bibliographic Source(s)

Cabrera AR, Kirkpatrick JP, Fiveash JB, Shih HA, Koay EJ, Lutz S, Petit J, Chao ST, Brown PD, Vogelbaum M, Reardon DA, Chakravarti A, Wen PY, Chang E. Radiation therapy for glioblastoma: an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. *Pract Radiat Oncol.* 2016;1-58. [210 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The American College of Physicians (ACP) process for assigning strength of recommendation (Strong, Weak) and grading of quality of evidence (High- [HQE], Moderate- [MQE], and Low-Quality [LQE]) is defined at the end of the "Major Recommendations" field.

Key Question (KQ) 1: When is radiation therapy indicated after biopsy/resection of glioblastoma and how does systemic therapy modify its effects?

Guideline Statements

- A. Fractionated radiotherapy improves overall survival compared to chemotherapy or best supportive care alone following biopsy or resection of newly diagnosed glioblastoma (HQE). Whether radiotherapy is indicated in a particular individual may depend on patient characteristics such as performance status (see KQ2). (Strong recommendation)
- B. Adding concurrent and adjuvant temozolomide to fractionated radiotherapy improves overall survival and progression-free survival compared to fractionated radiotherapy alone, with a reasonably low incidence of early adverse events and without impairing quality of life (HQE). The guideline panel endorses fractionated radiotherapy with concurrent and adjuvant temozolomide as the standard of care following biopsy or resection of newly diagnosed glioblastoma in patients up to 70 years of age (see KQ2 for recommendations regarding patients older than 70). (Strong recommendation)
- C. Adding bevacizumab to standard therapy for newly diagnosed glioblastoma (i.e., fractionated radiotherapy with concomitant and adjuvant temozolomide) does not improve overall survival and is associated with a higher incidence of early adverse events (HQE). Bevacizumab may, however, prolong progression-free survival (MQE). The panel does not recommend the routine addition of bevacizumab to standard therapy for newly diagnosed glioblastoma outside of a clinical trial. (Strong recommendation)

- D. The addition of other systemic therapies to conventional radiotherapy with or without temozolomide remains investigational. (Strong recommendation)

KQ 2: What is the optimal dose-fractionation schedule for external beam radiation therapy after biopsy/resection of glioblastoma and how might treatment vary based on pretreatment characteristics such as age or performance status?

Guideline Statements

- A. For patients under 70 with good performance status (Karnofsky performance status [KPS] ≥ 60), the optimal dose-fractionation schedule for external beam radiation therapy following resection or biopsy is 60 Gy in 2-Gy fractions delivered over 6 weeks (HQE). Numerous other dose schedules have been explored without definitive benefit. Care should be taken to keep dose to critical structures (e.g., brainstem, optic chiasm/nerves) within acceptable limits. (Strong recommendation)
- B. Older age and poor performance status are associated with shorter survival in glioblastoma patients (MQE). Prognostic considerations should help guide treatment recommendations for individual patients. (Strong recommendation)
- C. Among elderly patients (≥ 70 years old) with fair-good performance status (KPS ≥ 50), the panel recommends external beam radiation therapy following biopsy or resection, as radiotherapy (compared to supportive care alone) improves overall survival without impairing quality of life or cognition (HQE). The efficacy of concurrent and adjuvant temozolomide in this population has not been evaluated in a randomized trial, but may be considered for selected patients (LQE; see KQ2F). (Strong recommendation)
- D. Among elderly patients, there is no evidence that conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) is more efficacious than hypofractionated radiotherapy (e.g., 40 Gy in 15 fractions over 3 weeks) (HQE). Compared to conventionally fractionated radiotherapy, hypofractionated radiotherapy has been associated with superior survival and less corticosteroid requirement (MQE). (Strong recommendation)
- E. Given the absence of proven superiority for conventionally fractionated radiotherapy, the panel recommends hypofractionated radiotherapy for elderly patients with fair-good performance status (HQE). Temozolomide monotherapy is an efficacious alternative for elderly patients with O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (HQE), but the panel does not recommend temozolomide monotherapy as first-line therapy for patients with unmethylated MGMT promoters (MQE). Temozolomide monotherapy confers a higher risk of adverse events than radiotherapy, particularly with respect to hematologic toxicity, nausea, and vomiting (MQE). (Strong recommendation)
- F. Among elderly patients with good performance status, adding concurrent and adjuvant temozolomide to hypofractionated radiotherapy appears to be safe and efficacious without impairing quality of life (LQE). In such patients, the panel recommends consideration of concurrent and adjuvant temozolomide. The combination of hypofractionated radiotherapy and temozolomide may be particularly efficacious in those with a methylated MGMT promoter (LQE). (Strong recommendation)
- G. Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care (LQE). (Strong recommendation)

KQ 3: What are the ideal target volumes for curative-intent external beam radiotherapy of glioblastoma?

Guideline Statements

- A. Although glioblastoma is thought to be diffusely infiltrative, partial brain radiation therapy leads to no worse survival than whole brain radiation therapy (HQE). The panel endorses partial brain radiation therapy as the standard treatment paradigm for glioblastoma. (Strong recommendation)
- B. Several strategies for target volume definition produce similar outcomes (LQE). All confer a low risk of isolated marginal or distant failure, with a high risk of local failure as a component of disease progression (MQE). Acceptable strategies include but are not limited to the following (Strong recommendation):
1. Two-phase: 1) primary target volume encompasses edema (hyperintense region on T2 or fluid attenuation inversion recovery [FLAIR] on magnetic resonance imaging [MRI]) and gross residual tumor/resection cavity; 2) boost target volume encompasses gross residual tumor/resection cavity. A range of acceptable clinical target volume margins exists.
 2. One-phase: single target volume includes gross residual tumor/resection cavity with wide margins, without specifically targeting edema.
- C. Reducing target volumes allows less radiation to be delivered to radiographically normal brain. Delivering less radiation to normal brain should result in less late toxicity (LQE), but this remains to be validated. (Weak recommendation)

KQ 4: What is the role of reirradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?

Guideline Statements

In younger patients with good performance status, focal re-irradiation (e.g., stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, brachytherapy) for recurrent glioblastoma may improve outcomes compared to supportive care or systemic therapy alone (LQE). Tumor size and location should be taken into account when deciding whether re-irradiation would be safe (LQE). (Weak recommendation)

Definitions

ACP Process for Grading of Quality of Evidence

High-Quality Evidence

Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

Moderate-Quality Evidence

Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence

Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose–response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

ACP Process for Assigning Strength of Recommendation

Strong Recommendation

Evidence suggests that the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus.

Weak Recommendation

Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or non-uniform consensus.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Glioblastoma

Guideline Category

Management

Treatment

Clinical Specialty

Geriatrics

Neurology

Oncology

Radiation Oncology

Intended Users

Physicians

Guideline Objective(s)

- To systematically review the evidence for effective treatment of glioblastoma (GBM), focusing on the role of radiation therapy and the ways in which systemic therapies modify its effects
- To focus on the evidence for ideal dose-fractionation and target volume design
- To account for tumor-specific and patient-specific factors, including cytogenetics, performance status, and age, and the potential role of re-irradiation in recurrence

Target Population

Adults (age ≥ 18 years) with glioblastoma who have completed biopsy and/or resection or have recurrent disease

Interventions and Practices Considered

1. Conventionally fractionated or hypofractionated radiation therapy
2. Addition of concurrent and adjuvant temozolomide
3. Addition of bevacizumab to the standard therapy (not recommended routinely)
4. External beam radiation therapy (EBRT) following biopsy or resection
5. Temozolomide monotherapy as an alternative in some patients
6. Best supportive care
7. Use of partial brain irradiation for radiation delivery
8. Strategies for target volume definition: 2 phases (primary and boost volumes) or 1 phase (single volume)
9. Focal reirradiation for recurrent glioblastoma

Major Outcomes Considered

- Overall and progression-free survival
- Recurrence rates
- Toxicity
- Quality of life (QOL)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Description of Methods Used to Collect/Select the Evidence

Literature Review

A systematic review of the literature was performed in early 2014 to form the basis of the guideline. An analytic framework incorporating the population, interventions, comparators, and outcomes (PICO) was first used to develop and refine search strategies for each key question (KQ). The searches were conducted in MEDLINE PubMed and designed to identify studies published in English between January 1966 and February 2014 that evaluated adults with glioblastoma who had completed biopsy and/or resection (KQs 1-3) or had recurrent disease (KQ4). Both MeSH terms and text words were utilized and terms common to all searches included: *glioblastoma*, *malignant glioma*, *high-grade glioma*, *anaplastic glioma*, *radiation*, and *radiotherapy*. Additional terms specific to each KQ were also incorporated. The outcomes of interest were overall and progression free survival, recurrence rates, toxicity, and quality of life. The initial literature review was conducted in January 2014 and a second round of searches was carried out in February 2014, following revision of the search strategies to include additional terms. The electronic searches were supplemented by hand searches of the reference lists of previous systematic reviews and other relevant papers.

A total of 3,059 abstracts were retrieved. The articles were then reviewed by American Society for Radiation Oncology (ASTRO) staff, the co-chairs of the guideline, and the writing groups for each KQ. During the first round of screening, 2163 articles were eliminated based on the inclusion and exclusion criteria. The inclusion criteria were: patients ≥ 18 years of age, primary or recurrent glioblastoma, treatment with radiation therapy (including external beam radiation therapy [EBRT], brachytherapy, and stereotactic radiosurgery) with or without systemic therapy, and publication date 1966 to 2014. The exclusion criteria were: pre-clinical or non-human studies, case reports/series, non-English language, available in abstract only, pediatric patients, low-grade gliomas, absence of clinical outcomes reported, and otherwise not clinically relevant to the key clinical questions. Retrospective studies were also excluded for KQ1 as the presence of abundant prospective data obviated the need to include retrospective literature. The included articles subsequently underwent a second round of screening to select the most relevant studies and a further 739 articles were excluded during this stage, primarily due to poor relevance and/or poor quality. Ultimately, 157 full-text articles were chosen for inclusion and abstracted into detailed literature tables to provide supporting evidence for the clinical guideline recommendations.

Conference abstracts from ASTRO, American Society of Clinical Oncology, Society for Neuro-Oncology, and American Association of Neurological Surgeons meetings between 2011 and 2014 (as of July 2014), were separately reviewed but were not used to support the recommendation statements. This was done to ensure that no practice changing trials had been reported in abstract form that would have substantially changed or rendered obsolete any of the guideline's recommendations.

Number of Source Documents

One hundred fifty-seven full-text articles were chosen for inclusion and abstracted into detailed literature tables to provide supporting evidence for the clinical guideline recommendations.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

American College of Physicians (ACP) Process for Grading of Quality of Evidence

High-Quality Evidence

Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

Moderate-Quality Evidence

Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the

treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence

Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

For each guideline statement, the strength of the recommendations and the quality of supporting evidence were rated using the *American College of Physicians (ACP) Process for Assigning Strength of Recommendation and Grading of Quality of Evidence*. The evidence supporting respective guideline statements was rated high-quality evidence (HQE), moderate-quality evidence (MQE), or low-quality evidence (LQE) (see the "Rating Scheme for the Strength of the Evidence" field). The ratings were initially assigned by the chairs of the guideline and were later approved by all panel members.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

The guidelines subcommittee of the Clinical Affairs and Quality Council identified use of radiotherapy in glioblastoma (GBM) in both primary and recurrent settings as a high-priority topic in need of an evidence-based practice guideline. In accordance with established American Society for Radiation Oncology (ASTRO) policy, the guidelines subcommittee recruited a guideline panel of recognized experts in GBM including radiation oncologists, neuro-oncologists, a neurosurgeon, and patient and caregiver representatives. The guideline panel members were drawn from academic settings, private practice, and residency. Four key questions (KQs) were proposed, which addressed the role of external beam radiation therapy after biopsy/resection (KQ1), the optimal dose-fractionation (KQ2), the ideal target volumes (KQ3), and the role of re-irradiation in recurrent GBM (KQ4). In September 2013, the ASTRO Board of Directors approved the proposal and panel membership.

Through a series of conference calls and emails between December 2013 and September 2015, the guideline panel, with ASTRO staff support, completed the systematic review, created literature tables, and formulated the recommendation statements and narratives for the guideline. The members of the panel were divided by KQ into four writing groups, according to their areas of expertise.

Grading of Evidence, Recommendations, and Consensus Methodology

Guideline recommendation statements were developed based on the body of evidence and, when available, high-quality evidence formed the basis of the statements in accordance with Institute of Medicine (IOM) standards. The level of consensus among the panelists on the recommendation statements was evaluated through a modified Delphi approach. An online survey was sent by ASTRO staff to the panel members, who independently rated their agreement with each recommendation on a five-point Likert scale, ranging from strongly disagree to strongly agree (higher score corresponds with stronger agreement). A pre-specified threshold of $\geq 75\%$ of raters was determined to indicate when consensus was achieved. Following the survey, the panel reviewed the results, which were provided in aggregate only. Changes were made to three

recommendation statements to increase panel consensus. Using the same process, a second survey was sent to assess agreement on the revised statements.

For each guideline statement, the strength of the recommendations and the quality of supporting evidence were rated using the *American College of Physicians (ACP) Process for Assigning Strength of Recommendation and Grading of Quality of Evidence* (see the "Rating Scheme for the Strength of the Evidence" and "Rating Scheme for the Strength of the Recommendations" fields). Whether particular recommendations were rated "strong" or "weak" depended on the evidence clarifying the balance of risks and benefits (where applicable) and on the level of consensus established on the survey described above.

Rating Scheme for the Strength of the Recommendations

American College of Physicians (ACP) Process for Assigning Strength of Recommendation

Strong Recommendation

Evidence suggests that the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus.

Weak Recommendation

Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or non-uniform consensus.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The initial draft of the manuscript was reviewed by four expert reviewers and American Society for Radiation Oncology (ASTRO) legal counsel. A revised draft was placed on the ASTRO Web site for public comment in August and September 2015. Following integration of the feedback, the document was submitted for approval to the ASTRO Board of Directors in January 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Although the prognosis for glioblastoma (GBM) remains poor, therapeutic advances fueled by a large body of research have improved survival and quality of life. Optimal treatment is multidisciplinary and radiation therapy occupies an integral role, given GBM's proclivity for local recurrence.

Refer to the original guideline document for a discussion of evidence of benefits for specific statements.

Potential Harms

- In elderly patients, temozolomide monotherapy confers a higher risk of adverse events than radiotherapy, particularly with respect to hematologic toxicity, nausea, and vomiting.
- Bevacizumab may cause potentially severe adverse effects, including gastrointestinal perforation, wound healing complications, hemorrhage, and blood clots.
- Radiation necrosis is a well-documented toxicity from upfront chemoradiation, and salvage reirradiation adds to the risk. Several of the early studies involving single-fraction stereotactic radiosurgery reported high rates of late complications requiring re-operation (20%-40%).
- Conventional imaging (i.e., MRI) is limited in its ability to distinguish local recurrence from radiation-related changes. These challenges may bias attempts to analyze patterns of failure. Most patterns of failure studies have relied on institutional criteria to define progression, and in some cases it is possible that treatment effect (pseudoprogression) was interpreted as tumor progression. False positive errors are most likely to occur in the high-dose volume, biasing patterns of failure data.

Refer to the original guideline document for additional discussion of evidence of harms for specific statements.

Qualifying Statements

Qualifying Statements

- American Society for Radiation Oncology (ASTRO) guidelines present scientific, health, and safety information and may reflect scientific or medical opinion. They are available to ASTRO members and the public for educational and informational purposes only. Commercial use of any content in this guideline without the prior written consent of ASTRO is strictly prohibited.
- Adherence to this guideline will not ensure successful treatment in every situation. This guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods reasonably directed to obtaining the same results. The physician must make the ultimate judgment regarding any specific therapy in light of all circumstances presented by the patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. This guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials.
- This guideline was prepared on the basis of information available at the time the panel was conducting its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to revisit and update the guideline.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Cabrera AR, Kirkpatrick JP, Fiveash JB, Shih HA, Koay EJ, Lutz S, Petit J, Chao ST, Brown PD, Vogelbaum M, Reardon DA, Chakravarti A, Wen PY, Chang E. Radiation therapy for glioblastoma: an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. *Pract Radiat Oncol.* 2016;:1-58. [210 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016

Guideline Developer(s)

American Society for Radiation Oncology - Professional Association

Source(s) of Funding

American Society for Radiation Oncology

Guideline Committee

Glioblastoma Guideline Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Conflict of Interest Disclosure Statement

Before initiating work on this guideline, all panelists completed disclosure statements and pertinent disclosures are published within this report. Where potential conflicts are detected, remedial measures to address them are taken and noted here.

JK: Research funding, honoraria, and travel expenses from Varian, partner in ClearSight Radiotherapy Products, previous research funding from Genentech. JF: Honoraria, travel expenses, and research funding from Varian. HS: Advisory board for Genentech (started 10/2015), previous honoraria and travel expenses from Merck. EK: Research funding from Phillips, pending patent on quantitative pancreatic image analysis. SL: Previous stock in Tosk and Oculus. MV: Consultant for NeuralStem; stock options, royalties, and patent licensing and copyright fees from Infuseon. DR: Advisory boards for Roche/Genentech, EMD Serono, Novartis, Amgen, Abbvie, Bristol-Myers Squibb, Cavion, Celldex, Juno Pharmaceuticals, Momenta Pharmaceuticals, Novocure, Oxigene, Regeneron, and Stemline; previous advisory board for Apogenix; speaker bureaus for Merck/Schering and Roche/Genentech; research funding from Celldex, Inovio, and Midatech. PW: Advisory boards for Roche/Genentech, Novartis, Regeneron, Monteris, and Cavion; speaker for Merck; steering committee chair for Vascular Biogenics trial; previously on advisory boards for Abbvie, Cubist, Foundation Medicine, and Midatech. EC: Honoraria from Abbvie, BrainLab and Elekta.

The panel chairs and the American Society for Radiation Oncology (ASTRO) Guidelines Subcommittee reviewed these disclosures and took measures to mitigate the impact of potential conflicts. Due to relationships with Merck, Drs. Reardon, Shih, and Wen did not write the recommendations and narrative addressing temozolomide and were recused from consensus voting on these recommendations. Because of relationships with Genentech, Drs. Reardon, Wen and Kirkpatrick did not write the recommendations and narrative regarding bevacizumab and were recused from voting on these recommendations. No other disclosures were viewed as impacting guideline content.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [Practical Radiation Oncology Web site](#) .

Availability of Companion Documents

The following is available:

- Cabrera AR, Kirkpatrick JP, Fiveash JB, Shih HA, Koay EJ, Lutz S, Petit J, Chao ST, Brown PD, Vogelbaum M, Reardon DA, Chakravarti A, Wen PY, Chang E. Radiation therapy for glioblastoma: Executive summary of an American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. *Pract Radiat Oncol*. 2016 Jul-Aug;6(4):217-25. Available from the [Practical Radiation Oncology Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 31, 2016. The information was verified by the guideline developer on December 2, 2016.

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